



3  
WO 99/58095

1/PRTS  
09/700120  
529 Rec'd PCT/PTC 08 NOV 2000  
PCT/IB99/00862

PHARMACEUTICAL, HYGIENIC AND/OR COSMETIC COMPOSITIONS  
CONTAINING SEA WATER AND USES

*Ms 411*  
The present invention relates to the field of therapeutic chemistry and more specifically to that of pharmacy, hygiene and/or beauty care.

The present invention concerns a pharmaceutical, hygienic and/or cosmetic composition containing sea water and a basic amino acid or one of its salts or one of its esters. The main basic amino acids are arginine, lysine, citrulline or ornithine.

The pharmaceutical, hygienic and/or cosmetic compositions in accordance with the invention display an inhibitory effect on the activation of mastocytes induced by neuropeptides. In particular, the compositions according to the invention display an inhibitory action on the degranulation of mastocytes induced by substance P. Consequently, these compositions show anti-inflammatory and/or anti-allergic effects and can be used for the prevention and/or the treatment of ailments linked to a release of histamine.

The skin and the mucous membranes are the site of multiple attacks to which they respond with an inflammatory reaction. Therefore, nociceptive stimuli (temperature, mechanical stimuli, chemical irritants, allergens, UV..) cause the release of neuromediators, and in particular substance P. These substances are capable of inducing an inflammatory reaction which is thus said to be <<neurogenic>>. It is important to note that neurogenic inflammation is in fact a component in any inflammation whatever its cause (Ratzlaff et al, 1992, J. Neuroimmunol. 41:89-96). Consequently, any substance capable of interfering with the effects of substance P is likely to have an anti-inflammatory, anti-allergic, de-sensitising and analgesic effect.

Neurokinines are part of a family of peptides that are liberated by the sensory nerves. This family includes the substance P, the neurokinines A and B. The neurokinines as well as CGRP (calcitonin gene related peptide) and VIP (vasoactive intestinal peptide), are mediators of the NANC (non-adrenergic, non-cholinergic) peripheral

09/700120

4

WO 99/58095

PCT/IB99/00862

nervous system. All these peptides can be released by sensory nerve fibres (C fibres) which innervate the skin. They are mainly inflammatory mediators. Released into the skin, the neurokinines, and notably bradykinin, induce itching, red blotches, oedema... These symptoms are mainly linked to the release of histamine by substance P from the cutaneous mastocytes.

Substance P has a stimulant effect on the proliferation of lymphocytes, the synthesis of immunoglobulins, the degranulation of mastocytes, the phagocytosis of macrophages, chemotaxis and the release of mediators by the neutrophils. Substance P is therefore a very important factor in neurogenic inflammation. Intradermal injection of substance P in man or animals (mice, guinea pig) causes erythema in a few minutes. At the injection site, histological study reveals a significant increase in the number of intra- and perivascular neutrophils and eosinophils. The mechanism of this accumulation of inflammatory cells in the skin seems to imply two routes (Smith et al, 1993, J. Immunol. 151:3274-3282). On one hand, substance P induces the degranulation of cutaneous mastocytes thus causing the release of inflammation mediators such as histamine and chemotactic mediators for the polynucleates (LTB<sub>4</sub>, Paf-acether). On the other hand, substance P increases the expression of adhesion molecules by the microvascular endothelial cells of the dermis, and induces the liberation of pro-inflammatory cytokinins by the mastocytes. A large part of the inflammatory effects of substance P in the skin are therefore linked with the degranulation of cutaneous mastocytes (serous type mastocytes). Histological and ultrastructural studies have shown that the C fibres were in close contact with the cutaneous mastocytes. The liberation of substance P and histamine therefore mutually amplify each other in a self-maintained loop.

According to the present invention, the applicant has discovered, in an unexpected manner, that sea water taken alone, as well as the basic amino acid taken alone, each show an inhibitory action on the activation of mastocytes induced by neuropeptides, and, in particular an inhibitory action on the degranulation of mastocytes induced by substance P. Consequently, sea water, as well as a basic amino acid is an inhibitor of the release of histamine induced by substance P. In addition, the applicant has

5  
WO 99/58095

PCT/IB99/00862

discovered, in a totally unexpected manner that the combination of these two constituents shows a clear synergic effect on the activation of mastocytes induced by neuropeptides, and, in particular on the inhibition of the degranulation of mastocytes induced by substance P.

Therefore, the compositions conforming to the invention and notably those containing the combination of sea water-basic amino acid constitute, thanks to their inhibitory action on the release of histamine, an important technical advancement in the treatment of allergic and/or inflammatory symptoms.

In fact, allergy and inflammation (especially cutaneous), still currently poses numerous problems for therapists who only have a limited number of active substances at their disposal. In addition, some of these substances, like corticosteroids for example, can have often damaging side effects (atrophy, skin ageing, mycotic or bacterial infections etc.)

The present invention has more particularly as its object, a pharmaceutical, hygienic and/or cosmetic composition intended mainly to inhibit the degranulation of mastocytes characterised in that it contains sea water and a basic amino acid or one of its salts or esters, or a plant and/or animal extract containing, combined or mixed with an inert non toxic carrier or excipient, suitable for the envisaged application.

It also has as its object the use of sea water with a view to the achievement of a pharmaceutical, hygienic and/or cosmetic composition mainly intended to inhibit the activation of mastocytes, in particular degranulation.

It also has as its object the use of a basic amino acid, and notably arginine or one of its salts or esters, or a plant and/or animal extract containing, with a view to the achievement of a pharmaceutical, hygienic and/or beauty care composition intended mainly to inhibit the activation of mastocytes, in particular degranulation.

Basic amino acids have a number of pharmacological properties. The main example is arginine, which is a natural amino acid with a guanidine residue. It is, under the effect

6  
WO 99/58095

PCT/IB99/00862

of NO-synthase, at the origin of the formation of nitrogen monoxide. L-arginine is known for its bio-energy and anti-asthenic properties as a stimulant of the biosynthesis of growth hormone, against the senescence of crystalline, as well as for fighting against hyperammonemia and its consequences.

According to the invention, arginine used can be of natural or synthetic origin.

An example of plant and/or animal extract containing a basic amino acid is algae extract, an extract of marine, thermal or lake mud, or bacterial extract. These plant and/or animal extracts come notably from peloids. Therefore, compositions containing sea water combined for example with marine mud extracts, are, in the measure that these extracts contain a basic amino acid, notably arginine, in accordance with the invention.

Arginine, when obtained naturally, is in the levogyre form (L-arginine). The arginine preferably used in the present invention is L-arginine. Arginine can also be obtained synthetically, in the racemic form. According to the invention DL-arginine or even D-arginine could be used. Arginine can either be used in its own form or in the form of one of its pharmaceutically and/or cosmetically acceptable salts or esters. Amongst the salts of arginine, mono- or dihydrochloride, mono- or dihydrobromide, sulphate, glutamate, pidolate or hydrochloride can be cited. Amongst the esters the methyl or ethyl ester of these can be cited.

The sea water used in the present invention is mainly taken from seas or oceans, but also in resurgences or infiltrations where sea water circulates. It can be filtered and sterilised by additional sterilising filtration.

The seas and oceans are the Atlantic or the English Channel for example. The sea water is filtered through a filter fine enough to eliminate the solid particles in suspension, and it is sterilised by passage through a sterilising membrane.

The sea water filtered and sterilised in this way can then, according to the uses envisaged, be made isotonic by dilution or de-ionisation.

The sea water can be de-ionised by selective adsorption of sodium and/or replacement of the sodium by another metallic ion like calcium or magnesium. The calcium and/or magnesium salt content of the sea water can be increased in this way at the same time as reducing the sodium or potassium salt content. The content of bromate and bromide

00441621000000

7  
WO 99/58095

PCT/IB99/00862

can be modified in the same way.

Each DI  
In the compositions in accordance with the invention, containing the sea water-basic amino acid combination, the quantity of sea water represents from 30 to 99% of the total weight of the composition. More particularly, the quantity of sea water represents from 60 to 95% of the total weight of the composition. The quantity of basic amino acid in the compositions containing the sea water-basic amino acid combination, represents 0.0001% to 10% of the total weight of the composition. More particularly, the quantity of basic amino acid represents from 0.0005 to 2% of the total weight of the composition.

However, when sea water alone is used, or inversely when basic amino acid alone is used, with a view to the production of a pharmaceutical, dietary and/or cosmetic composition intended mainly to inhibit the degranulation of mastocytes, the percentages will be different.

The methods given below refer more particularly to the composition as previously defined, containing sea water and a basic amino acid like arginine.

However, these methods are equally applicable when sea water alone is used, or inversely when basic amino acid alone is used, with a view to the production of a pharmaceutical, hygienic and/or cosmetic composition mainly intended to inhibit the degranulation of mastocytes.

Furthermore, the composition according to the invention could be combined with additional active ingredients intended notably for the prevention and/or treatment of inflammatory and/or allergic ailments. Therefore, the composition is again characterised in that it contains at least one agent selected from antibacterial, anti-parasitic, anti-fungal, anti-pruritogenic, anti-free radical, anaesthetic, antiviral, anti-dandruff, anti-acne, anti-seborrheic, agents, vitamins and/or healing agents, and/or agents preventing or treating ageing (of the skin, the gums,...), and softener agents.

The composition in accordance with the invention can moreover contain a pH-regulating agent.

The pH of the composition in accordance with the invention is regulated within a zone



9  
WO 99/58095

PCT/IB99/00862

emulsion. The compositions according to the invention could be administered in the form of patches.

The method of administration envisaged could be cutaneous, oral, percutaneous, parenteral, nasal, ocular, oral, gingival, bronchial, vaginal, rectal... Nevertheless, the excipients used are those which are normally appropriate according to the method of administration and the usage envisaged.

The composition according to the invention is preferably intended to be applied on the skin (on any cutaneous area of the body) and the mucous membranes, in particular the nasal or ocular mucous membranes.

Therefore, for an application with a therapeutic aim for the eyes, the compositions of the invention can be presented in the form of eye lotion, ointment or washing solution.

Amongst the basic amino acids of the invention, it may more particularly be cited :

- Those with a guanidine function, like arginine or homarginine;
- Those with an amino function, like lysine, diaminopimelic acid or diaminovaleric acid;
- Those with a quaternary ammonium function like carnitine, homarine;
- Those substituted by a methyl, like  $\alpha$ -methyl *m*-tyrosine or N-methylaspartic acid;
- Those substituted by a carboxamide grouping, like ornithine;
- Those substituted by a cyano group;
- Those substituted by a methylamino group, like sarcosine;
- Those substituted by a phosphonic group.

#### EXPERIMENTAL PARTS

Study of the action of sea water alone, arginine alone, and of the composition containing sea water and arginine together on the release of histamine.

##### 1) Model in vitro

Here the inhibitory effects of sea water alone, of arginine alone, and, sea water supplemented by arginine on neurogenic inflammation are studied. Whether sea water supplemented with arginine inhibits the degranulation of peritoneal rat mastocytes

001122 "00112200200



10  
WO 99/58095

PCT/IB99/00862

induced by substance P, and whether the said sea water supplemented with L-arginine has a clear synergic effect in relation to each of the two constituents taken alone is thus studied in this way in vitro.

The peritoneal rat mastocytes are considered in pharmacology as a model for human cutaneous mastocytes.

a) Introduction

There are two distinct mastocytic sub-populations: <<mucous>> (previously called atypical) mastocytes present in the mucous membranes and the serous mastocytes (or <<mastocytes of the conjunctive tissue>>) present in the skin and the peritoneal cavity. These two sub-classes are different because of their localisation in the tissues, their histological, immunological and functional properties. The mastocytes of the peritoneal cavity in rats are a classical pharmacological model of human cutaneous mastocytes.

The activation of the mastocytes can not only make the stimulation of their specific IgE receptors occur, but also their reactivity to different peptides. Therefore, the peptidergic method of activation of the mastocytes constitutes the second method of physiological activation of these cells, apart from the method dependent on the IgE (antigenic method).

b) Experimental protocol

Peritoneal mastocytes in rats are obtained by washing after injection of Tyrode solution. The mastocytes represent from 8 to 10% of peritoneal cells made up equally of macrophages, lymphocytes and monocytes. The mastocytes are purified on a layer of metrizamide at 22.5% then placed again in a Tyrode solution.

Composition of the Tyrode solution (in mM):

- NaCl: 137
- KCl: 2.6
- Glucose: 5.6
- HEPES: 4.2
- CaCl<sub>2</sub>: 0.3

11  
WO 99/58095

PCT/IB99/00862

-Bovine albumin serum: 0.25%

The mastocytes are pre-incubated (5 min; 37°C in a bain-marie) with a control (Tyrode buffer), with different concentrations of sea water alone, arginine alone, or sea water supplemented with arginine, in the Tyrode buffer.

The mastocytes are then stimulated by substance P (5 min; 37°C). Perchloric acid (final 0.4N) is added onto the pellets and the cellular supernatants and then histamine are measured by a spectrofluorimetric method.

### c) Results

The results are given in table 1 below:

Table 1:

Percentage of histamine released	Arginine 0mM	Arginine 1mM	Arginine 3mM
0% sea water	55 ± 8	38 ± 6	19 ± 4
3% sea water	35 ± 7	22 ± 5	6 ± 3
10% sea water	6 ± 1	2 ± 1	1 ± 1
20% sea water	1 ± 0	1 ± 0	1 ± 0





Column 1 of table 1 represents the results obtained with the control, i.e. 0% sea water, 100% Tyrode solution, a concentration of sea water at 3%+97% Tyrode solution, a concentration of sea water at 10%+90% Tyrode solution, and, a concentration of sea water at 20%+80% Tyrode solution respectively. Column 2 represents the results obtained with the same concentrations (sea water/Tyrode solution) respectively as in column 1 with an addition of arginine in a concentration of 1mM. In the same way, column 3 represents the results obtained with the same concentrations (sea water/Tyrode solution) respectively as in column 1, with addition of arginine in a concentration of 3mM.

The results of table 1 are expressed in percentages of the release of histamine ±S.E.M.  
n = 6 experiments

12  
WO 99/58095

PCT/IB99/00862

Table 1 is represented by figure 1.

The symbols , , , of figure 1 represent:		
	0 % sea water (100% Tyrode Solution) (possibly supplemented by L-arginine)	
	3 % sea water (97 % Tyrode Solution)	(")
	10 % sea water (90% Tyrode Solution)	(")
	20 % sea water (80% Tyrode Solution)	(")

The percentage of histamine release induced by peptidergic stimulation is from  $55 \pm 8\%$ . In the presence of sea water alone, the release of histamine diminishes more or less strongly according to the concentration of sea water in the preparation. Therefore, for a 3% concentration of sea water in the preparation, the release of histamine is from  $35 \pm 7\%$ ; for a 10% concentration of sea water, the liberation of histamine is from  $6 \pm 1\%$  in the presence of a 20% concentration of sea water, the release of histamine is no more than  $1 \pm 0\%$ .

Therefore, even in the presence of a low percentage of sea water (3%), an inhibition of mastocytic degranulation can already be noted. The inhibition of histamine release is even greater the higher the concentration in sea water.

Similarly, in the presence of arginine alone, the release of histamine also diminishes. Therefore, in the presence of arginine alone in a concentration of 1mM, the release of histamine is from  $38 \pm 6\%$ , and, in the presence of arginine alone at 3mM, the release of histamine is no more than  $19 \pm 4\%$ .

Therefore, the treatment of mastocytes by sea water alone, or by arginine alone, induces a dose-dependent inhibition of the degranulation of the mastocytes induced by substance P.

The treatment of mastocytes by the composition according to the invention, containing sea water and a basic amino acid like arginine, potentializes the inhibition of the release of histamine in relation to that observed when the cells are incubated only in the presence of sea water or arginine.

13  
WO 99/58095

PCT/IB99/00862

#### d) Conclusion

The inhibitory effects of sea water and a basic amino acid like arginine potentialize mutually. Experimentally an accrued efficiency of the said combination on the inhibition of the degranulation of mastocytes in relation to that of sea water alone or arginine alone, is noticed.

Table II hereafter takes the previous results provided in table I on the inhibition of the release of histamine by sea water after induction by substance P.

These results are completed:

- By the study of the inhibition of the degranulation of human basophils caused by anti IgE serum;
- By the study of the degranulation of peritoneal mastocytes in rats after induction by VIP; the inhibitory effect is totally dependent on the concentration in sea water;
  - By the study of the degranulation of peritoneal mastocytes in rats induced by CGRP; an already very significant inhibition is obtained at a concentration of 10% in sea water;
- By the study of the degranulation of peritoneal mastocytes in rats induced by bradykinin. Inhibition of the degranulation is almost total for a 10% concentration of sea water.

Table 2

Summary of the inhibition of the release of histamine by sea water		
<b>Peritoneal rat mastocytes (SP 10<math>\mu</math>M)</b>		
n=7	<b>Average</b>	<b>SEM</b>
SP	55.5 %	6.7 %
SP + EM 3 %	34.7 %	6.2 %
SP + EM 10 %	6.8 %	1.5 %
SP + EM 20 %	1.4 %	1.3 %
<b>Human basophils (anti-IgE 1/1000)</b>		
n=3	<b>Average</b>	<b>SEM</b>
a-IgE	52 %	9 %
a-IgE + sea water 3 %	26 %	2 %
a-IgE + sea water 10 %	17 %	2 %
a-IgE + sea water 20 %	10 %	1 %

14  
WO 99/58095

PCT/IB99/00862

<b>Peritoneal rat mastocytes (VIP 3<math>\mu</math>M)</b>		
n=4	<b>Average</b>	<b>SEM</b>
VIP	61 %	3 %
VIP + sea water 3 %	44 %	5 %
VIP + sea water 10 %	14 %	3 %
VIP + sea water 20 %	4 %	2 %
<b>Peritoneal rat mastocytes (CGRP 30<math>\mu</math>M)</b>	<b>exp 1</b>	
n=1		
CGRP	79 %	
CGRP + 10 % sea water	44 %	
<b>Peritoneal rat mastocytes (Bradykinin 30<math>\mu</math>M)</b>	<b>exp 1</b>	
n=1		
Bradykinin	67 %	
Bradykinin + 10 % sea water	7 %	

SP : substance P  
EM : sea water  
VIP : Vasoactive Intestinal Peptide

## II) Model in vivo

### 1. Effect of the composition containing the sea water / arginine combination on an in vivo model of cutaneous extravasation.

#### a) Introduction

The sub-cutaneous injection of substance P in the rat or guinea pig produces an inflammation of the skin of the back which found expression by cutaneous vasodilation and extravasation of plasmatic proteins. This neurogenic inflammation model allows to test substances with an anti-allergic and/or anti-inflammatory objective. Plasmatic extravasation linked to neurogenic inflammation is evidenced by Evans blue.

#### b) Experimental protocol

The backs of guinea pigs (Hartley males, 300g) are shaved and an isotonic solution of Evans blue is injected into the vein of the penis. One hundred  $\mu$ l of substance P (0.62 $\mu$ mol) are diluted into physiological serum with or without a solution of sea water at 10% and arginine (1 $\mu$ mol) and are injected into different sub-cutaneous sites. Plasmatic extravasation is observed by the bluish colouring of the teguments.

#### c) Results

15  
WO 99/58095

PCT/IB99/00862

The results are illustrated by table 3. The crosses symbolise the intensity of the bluish colouring of the teguments.

Table 3:

Stimulus	Intensity of the coloured reaction
Substance P (SP)	+++
SP + sea water 10%	++
SP + sea water 10% + arginine	+

d) Conclusion

Sea water at 10% reduces extravasation induced by substance P. This effect is potentialized by arginine.

2. Trial <<in vivo>>

Evaluation of the anti-inflammatory effect on the neurogenic inflammation induced by the electric stimulation of the saphena vein in rats.

a) Principle

Any possible neurogenic anti-inflammatory effect of sea water enriched with arginine on the neurogenic inflammation induced by electric stimulation of the saphena vein were evaluated in the anaesthetised rat. The test consists of inducing neurogenic inflammation by stimulation of the saphena vein, this nerve innervating the cutaneous area of the hind leg. Its stimulation induces the release, from the nerve endings of neuromediators responsible for neurogenic inflammation like substance P or CGRP. Neurogenic inflammation is evaluated by the measurement of the extravasation of Evans Blue which occurs in the course of inflammatory processes.

b) Experimental method

Male Wistar rats with an average weight of 250g were housed in air-conditioned cages of standard dimensions.

The animals were divided into four groups:

16  
WO 99/58095

PCT/IB99/00862

- group 1 is a control group receiving bi-distilled water;
  - Group 2 is a control group for the method which receives a control substance (Spantide II) which is an antagonist of substance P at a dose of 30 nmol/animal;
  - and group 3 is a group which receives sea water enriched with a basic amino acid.

The day before the trial (day 4) the animals were treated with guanethidine (20mg/Kg s.c. at a dose of 1mg/Kg to avoid any interaction with catecholamines.

The day of the trial (day 5), the animals received the anticipated product according to the randomisation plan, then they were anaesthetised with pentobarbital (60mg/Kg IP at a dose of 1mg/Kg). About 15 minutes after the end of the treatment, a solution at 2.5% of Evans Blue in saline was injected intravenously (1mg/Kg). Immediately afterwards, the saphena vein of the right hind leg was stimulated (15v, 2Hz, 1mS) for 15 minutes. The neurogenic inflammation induced by electric stimulation of the saphena vein was evaluated by the amount of extravasated Evans Blue. Oedema was also evaluated by the difference in weight of the cutaneous samples of the left (not stimulated) and right (-stimulated) hind leg.

The results obtained are gathered in table 4 hereafter. The percentage of variation is calculated in comparison with the control group which only receives bi-distilled water.

Table 4

TREATMENT	Extravasated Bleu Evans (µg/site)		OEDEMA (mg)
Bi-distilled water	Med.	8.13	46.50
	Mini.	4.61	-3.00
	Maxi.	16.68	69.40
	N	8	8
SPANTIDE II 30 nmoles	Med.	1.57	5.20
	Mini.	-0.19	-38.10
	Maxi.	2.97	27.80
	N	8	8
	P	**	*

PCT/LB99/00862

	%	-81	-89
Sea water + arginine	Med.	4.77	25.45
	Mini.	0.80	-5.80
	Maxi.	7.97	49.60
	N	8	8
	P	*	NS
	%	-41	-45

### c) Conclusion

The composition according to the invention also has a significant effect on oedema.

By healing agent of the hydrocolloid group is meant any mineral or organic substance likely to form a gel on contact with the skin or the mucous membranes and able to incorporate the preparation according to the invention.



18  
WO 99/58095

PCT/IB99/00862

The compositions according to the invention are intended for oral administration notably in the form of tablets or capsules after adsorption onto an inert carrier, for gingival administration in the form of toothpaste or liquid toothpaste, for vaginal administration, for ophthalmic administration in the form of eye lotions and auricular administration in the form of ear drops.

The sea water can indeed be used alone. The addition of a basic amino acid, and notably arginine, markedly reinforces the effects of sea water. The sea water acts on the mastocytes and on the basophils to inhibit their degranulation. It inhibits the effects of VIP, CGRP, and of Bradykinin.

Moreover, sea water alone inhibits the production of PGE<sub>2</sub> (prostaglandin E<sub>2</sub>) secreted by human keratinocytes.

The following examples of formulation illustrate the invention, they do not limit it in any way.

#### EXAMPLE I

##### Eye lotion

-Purified, sodium free and isotonic sea water	90%
-Arginine	2%
-Dextran Sulphate	1%
-Distilled water, preservative	qsp

#### EXAMPLE II

##### Softening emulsion for sensitive skin

-Purified, sterilised, sodium free and isotonic sea water	91%
-Arginine	2%
-Cosmetic emulsion for sensitive skin	q.s.p.
(fatty alcohol, polyoxyethylenated fatty alcohol, mineral oil, isopropyl palmitate, glycerine, thickener, preservatives, perfume, water)	

#### EXAMPLE III

19  
WO 99/58095

PCT/IB99/00862

Composition for oral administration

-Purified, sterilised sea water	450g
-Lysine hydrochloride	14g
-Hydroxyethylcellulose	7g
-Calcium carbonate	36g
-Magnesium silicate	5g
-Bentonite	40g

The purified sea water is adsorbed onto the bentonite + hydroxyethylcellulose mixture to obtain a pulverulent mass that is granulated then ground. Then the Lysine hydrochloride then the calcium carbonate and finally the magnesium silicate is added. The total mass is finally compressed into 1000 tablets with an average weight of 0.520g.

EXAMPLE IV

Composition for oral administration

-Purified, sterilised sea water	173g
-Arginine pidolate (commercially available under the trade name Argidone® (PCIB company)	60g
-Polyvinylpyrrolidone (Kollidon K90)	17g
-Polyethylene glycol 4000	120g
-Calcium carbonate	120g
-Talc	10g

The sea water and the arginine pidolate are adsorbed onto polyethylene glycol 4000. The resulting paste mixture is diluted with polyvinylpyrrolidone, then calcium carbonate. The thus obtained powder has Talc added and is compressed into tablets of an average weight of 0.500g.